Developing a Drosophila model to study neural stem cell derived tumors

Chrysanthi Voutyraki [1,2,#], **Evanthia Zacharioudaki** [1], **Srivathsa S. Magadi**[1], **Ioanna Poutakidou**[1], **Christina Efraimoglou**[1], **Gerasimos Anagnostopoulos**[1], **Margarita Stapountzi**[1] and **Christos Delidakis**[1,*]

[1] Institute of Molecular Biology and Biotechnology, FORTH, Heraklion, Greece

[2] Department of Biology, University of Crete, Heraklion, Greece

Presenting author: CV, email: cvoutyraki@gmail.com

* Corresponding author: XD, email: delidaki@imbb.forth.gr

ABSTRACT

One of the main characteristics of solid tumors (e.g neuroblastomas, medulloblastomas) is that they are heterogeneous containing, among others, cancer stem cells (CSCs). CSCs are able to self-renew and drive tumor growth. We are studying a tumor model in Drosophila, which may show similarities to CSC-based human solid tumors. Notch signaling is implicated in fine tuning the self renewal of neural stem cells (NSCs). Previous work in our lab has shown that Notch overactivation leads to hyperplastic phenotypes in the Drosophila central nervous system[1]. These phenotypes are mediated by the upregulation of a network of transcription factors, among which are the HES genes that promote stem cell fate and block differentiation. Indeed, HES upregulation is sufficient to induce NSC hyperplasias. The aim of this study is to assess the malignant potential of these Notch (N) or HES NSC hyperplasias and characterize their expression profile at various stages of tumor progression. To achieve this, we deploy an allograft technique (transplantation assay); larval N or HES induced hyperplastic CNS tissue fragments are transferred to the abdomen of healthy adult hosts. We have found that these aberrant tissues can overproliferate, colonize the abdomen, invade distal tissues and kill the host, suggesting that they have become malignant. To characterize the repertoire of deregulated genes and discover gene networks involved in malignant transformation and tumor aggressiveness, we are planning to perform transcriptome analysis at different tumor stages, including the primary hyperplasia and two metastatic tumors (first vs fourth passage in host flies).

Another aspect of studying the development of Notch-derived NSC malignancies is the characterization of how the microenvironment of a host organism interacts with the allografted tumor and whether it plays a role in its development. Our preliminary results show that hemocytes originating from the host are attached to the transplanted tumor and engulf cancer cells. Furthermore, these hemocytes can be transferred to new hosts upon serial passaging. What remains to be elucidated is the role of hemocytes on tumor growth; is it phagocytosis and elimination of the tumor mass, or cooperation towards tumor development, similar to the role of tumor associated macrophages (TAMs) in mammalian cancers? To investigate these two hypotheses, we have generated host flies with ablated or overproliferating hemocytes aiming to examine tumor growth at cellular resolution.

REFERENCES

[1] Zacharioudaki, E., Magadi, S. S. & Delidakis, C. bHLH-O proteins are crucial for Drosophila neuroblast self-renewal and mediate Notch-induced overproliferation. *Development* **139**, 1258–1269 (2012).